Combining Cytotoxic and Targeted Therapies for Lung Cancer

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In this issue, Heist et al.[1] present experience from a phase I to II trial of a combination of topotecan and targeted drug AT-101 for patients with small cell lung cancer in progression after first-line chemotherapy. Although the trial did not include a control group and the study population was relatively small, it nevertheless seems that this combination of a targeted drug and chemotherapy is not superior to chemotherapy alone.

A similar conclusion may be derived from five other studies on advanced non-small cell lung cancer with a total of more than 5000 patients. Two trials (INTACT 1 and INTACT 2) tested chemotherapy alone or in combination with gefitinib[2,3] and the other two (TRIBUTE and TALENT) tested chemotherapy with or without erlotinib.[4,5] In all four trials, adding a tyrosine kinase inhibitor to chemotherapy did not prolong the time to progression or overall survival. The fifth study is the recently published FLEX trial in which chemotherapy was given with or without cetuximab.[6] Addition of cetuximab led to moderate yet statistically significant prolongation of overall survival. However, there was an important difference in the duration of the treatment between the two arms: patients in the chemotherapy-only arm stopped all anticancer treatment after a maximum of 4 months, whereas the cetuximab arm continued with the targeted drug until progression. A close look at the data reveals overlapping survival curves during the first 6 months and their separation only after 8 months of treatment. Therefore, it remains uncertain whether the combination is truly superior to chemotherapy alone. It may well be that the advantage of the cetuximab arm in the FLEX trial was due to the benefit of prolongation of the primary treatment. In other words, it is not the superiority of the combination but longer duration of primary treatment that led to better survival—a phenomenon seen also in positive trials of maintenance or early second-line treatment with gemcitabine, pemetrexed, or erlotinib.[7–9]

After negative experience from these six trials, should we continue with efforts to combine chemotherapy and targeted drugs or should we abandon any further research in this direction? To approach this question, we have to see what all six trials have in common and try to answer why they failed. All six trials are similar in one parameter: they applied chemotherapy and targeted drugs simultaneously. Schedules that apply chemotherapy and targeted drugs simultaneously ignore one crucial aspect: potential antagonism between the two classes of drugs. Sensitivity to targeted drugs may well push tumor cells to the dormant phases of the mitotic cycle and render them resistant to classic cytotoxic agents. If this is true, then negative results from simultaneous use of cytotoxic drugs and targeted agents do not come as a surprise.

Time separation between chemotherapy and targeted drugs is an approach that avoids the aforementioned antagonism between the two classes of drugs. An additional advantage of such an intermittent schedule is prevention of tumor repopulation that occurs during the gap between individual applications of chemotherapy.[10] In vitro research has clearly demonstrated that schedules with different timing of chemotherapy and of targeted drugs lead to their synergistic or antagonistic antitumor activity.[11–13] Preliminary promising experience from clinical trials conducted in United States,[14] Hong Kong,[15] and

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Slovenia (M. Zwitter, unpublished data) supports the concept of intermittent schedules. Deeper understanding of general tumor biology, the characteristics of each individual tumor, and optimal timing of our interventions should lead to fewer disappointments in future clinical research.

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